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1.	Your reference	44.66174/000
2.	Patent application number *(The Patent Office will fill in this part)*	9711643.8 06JUN97 E279781-1 D00027 ~~P01/7700 25.00 - 9711643.8~~
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	Janssen Pharmaceutica NV Turnhoutseweg 30 B-2340 Beerse Belgium
	Patents ADP number *(if you know it)*	
	If the applicant is a corporate body, give country/state of incorporation	Belgium 05319394001
4.	Title of the invention	Glass Thermoplastic Systems
5.	Name of your agent *(if you have one)*	Frank B. Dehn & Co.
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	179 Queen Victoria Street London EC4V 4EL
	Patents ADP number *(if you know it)*	166001
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11. I/We request the grant of a patent on the basis of this application.

Signature   Date 5 June 1997

FRANK B. DEHN & CO.

12. Name and daytime telephone number of person to contact in the United Kingdom	Julian Cockbain 0171 206 0600

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COMPOSITIONS

This invention relates to novel pharmaceutical compositions, in particular compositions providing improved drug release and uptake on administration into externally voiding body cavities (e.g. the gi tract) or on topical administration, especially for acid solubilized drug compounds.

Many drug compounds, while possessing desired therapeutic properties, are used inefficiently due to their poor water solubilities. Thus for example where such compounds are administered orally, only a small fraction of the drug is taken up into the blood during transition of the gi tract. As a result, to achieve adequate drug uptake it may be necessary to administer high doses of the drug compound, to prolong the period of drug administration or to make frequent administrations of the drug compound. Indeed, the poor solubility and hence poor bioavailability of a drug may cause an alternative drug, perhaps one with undesired side effects or one which requires invasive administration (e.g. by injection or infusion), to be used in place of the poorly soluble drug.

One approach to poor solubility is to derivatise the drug molecule to introduce water solubilizing groups, e.g. ionic groups such as carboxyl groups or non-ionic groups such as polyhydroxyalkyl groups, so as to produce a more soluble derivative. This approach however is not always successful as it may not be possible to maintain adequately high therapeutic efficacy and adequately low toxicity or other side effects. Thus one example of a poorly water soluble drug which has not been superseded by a solubilized derivative is the antifungal agent itraconazole.

Attempts have therefore been made to enhance the uptake of drugs such as itraconazole by increasing the surface area of the drug compound exposed to saliva or gastric fluid, and hence promote dissolution of the drug compound, by thinly coating the drug compound onto essentially inert carrier particles, e.g. sugar beads. This however has the drawback that the volume of solid composition required to administer a given quantity of the drug compound is quite high since the carrier contributes significantly to the overall administration volume. Since administration of large volume capsules or tablets, or of large quantities of smaller volume capsules or tablets, provides difficulties for the patient, the drawbacks of this approach are obvious.

Yet another approach has been to administer the drug compound in the form of a solution of the drug compound and a drug complexing agent such as a cyclodextrin. This approach has limitations also in that the dosage volume is constrained by the solubilizing power of the complexing agent, readily unitized solid dosage forms can not be used, and there is no gradual release of the drug compound for biological uptake.

However, we have now found that by combining such drug compounds with a cyclodextrin, a water-soluble acid and a water-soluble organic polymer, an administration form may be produced which surprisingly improves the biological uptake of the drug compound, in particular a form which can surprisingly improve the time profile for the drug content of the plasma of the patient.

Thus viewed from one aspect the invention provides a pharmaceutical composition comprising a no more than sparingly water-soluble drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer.

Viewed from a further aspect the invention provides the use of a no more than sparingly water-soluble drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer for the manufacture of a pharmaceutical composition according to the invention for use in a method of therapy or diagnosis of the human or non-human animal (e.g. mammalian, reptilian or avian) body.

Viewed from a still further aspect the invention provides a method of therapy or diagnosis of the human or non-human animal (e.g. mammalian, reptilian or avian) body which comprises administering to said body a therapeutically or diagnostically effective dose of a pharmaceutical composition, the improvement comprising using as said composition a composition according to the present invention.

The compositions of the invention may if desired be aqueous, but in general will preferably be substantially water-free, e.g. containing up to 3% by weight, preferably less than 1% by weight water, and most preferably less than 0.5% water, but may be mixed with water immediately before administration or may be coated and dispersed in an aqueous medium whereby the coating is only broken down after administration. Such aqueous compositions are deemed to fall within the scope of the invention. Depending on the selection of components, the compositions of the invention may be liquid, solid or semi-solid - e.g. gel-like. Preferably the compositions are non-freeflowing at ambient temperature (e.g. 21°C), other than as free flowing particulates. Thus the compositions at ambient temperature are preferably solids or semi-solids or, less preferably, highly viscous fluids.

In the compositions of the invention the drug compound, acid, cyclodextrin and organic polymer are preferably intimately admixed.

Thus where the composition is particulate, the acid, drug compound, cyclodextrin and organic polymer are mixed together within the particles (e.g. at the molecular level following solvent removal from a solution of these components). Granulate mixtures where individual particles do not contain all four components, or have cores of one or more components coated with other components are not preferred. This intimate admixture is important since the effects of the components are complimentary at the microscopic level during dissolution of the compositions of the invention.

As the cyclodextrin in the compositions of the invention, there may be used any of the physiologically tolerable water-soluble substituted or unsubstituted cyclodextrins or physiologically tolerable derivatives thereof, e.g. α-, β- or γ-cyclodextrins or derivatives thereof, in particular derivatives wherein one or more of the hydroxy groups are substituted, e.g. by alkyl, hydroxyalkyl, carboxyalkyl, alkylcarbonyl, carboxyalkoxyalkyl, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl or hydroxy-(mono or polyalkoxy)alkyl groups, wherein each alkyl or alkylene moiety preferably contains up to six carbons.

Substituted cyclodextrins which can be used in the invention include polyethers, e.g. as described in US Patent 3,459,731. In general, to produce these, unsubstituted cyclodextrins are reacted with an alkylene oxide, preferably under superatmospheric pressure and at an elevated temperature, in the presence of an alkaline catalyst. Since a hydroxy moiety of the cyclodextrin can be substituted by an alkylene oxide which itself can

react with yet another molecule of alkylene oxide, the average molar substitution (MS) is used as a measure of the average number of moles of the substituting agent per glucose unit. The MS can be greater than 3 and theoretically has no limit. In the cyclodextrin derivatives for use in the compositions according to the present invention the M.S. is conveniently in the range of 0.125 to 10, in particular of 0.3 to 3, or from 0.3 to 1.5. Preferably the M.S. ranges from about 0.3 to about 0.8, in particular from about 0.35 to about 0.5 and most particularly it is about 0.4. M.S. values determined by NMR or IR preferably range from 0.3 to 1, in particular from 0.55 to 0.75.

Further examples of substituted cyclodextrins include ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyl or C_{1-6}-alkyloxy-carbonyl-C_{1-6}-alkyl groups or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}-alkyl, hydroxy-C_{2-4}-alkyl or carboxy-C_{1-2}-alkyl or more particularly by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl or carboxyethyl.

In the foregoing definitions, the term "C_{1-6}-alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as methyl, ethyl 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like.

Such ethers can be prepared by reacting a cyclodextrin with an appropriate O-alkylating agent or a mixture of such agents in a concentration selected such that the desired cyclodextrin ether is obtained. The reaction is

preferably conducted in a solvent in the presence of a base. With such ethers, the degree of substitution (DS) is the average number of substituted hydroxy functions per glucose unit, the DS being thus 3 or less.

In the cyclodextrin derivatives for use in the compositions according to the present invention, the DS preferably is in the range of 0.125 to 3, in particular 0.3 to 2, more particularly 0.3 to 1, and the MS is in the range of 0.125 to 10, in particular 0.3 to 3 and more particularly 0.3 to 1.5.

Of particular utility in the present invention are the β-cyclodextrin ethers, e.g. dimethyl-β-cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and polyethers, e.g. hydroxypropyl-β-cyclodextrin and hydroxyethyl-β-cyclodextrin. Such alkyl ethers may for example be methyl ethers with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example be formed from the reaction between β-cyclodextrin and propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

Especially suitable cyclodextrins are β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD.

Besides simple cyclodextrins, branched cyclodextrins and cyclodextrin polymers may also be used.

Other cyclodextrins are described for example in Chemical and Pharmaceutical Bulletin <u>28</u>: 1552-1558 (1980), Yakugyo Jiho No. 6452 (28 March 1983), Angew. Chem. Int. Ed. Engl. <u>19</u>: 344-362 (1980), US-3,459,731, EP-A-0,149,197, EP-A-0,197,571, US-4,535,152, WO-

90/12035 and GB-2,189,245. Other references describing cyclodextrins for use in the compositions according to the present invention, and which provide a guide for the preparation, purification and analysis of cyclodextrins include the following: "Cyclodextrin Technology" by József Szejtli, Kluwer Academic Publishers (1988) in the chapter Cyclodextrins in Pharmaceuticals; "Cyclodextrin Chemistry" by M.L. Bender et al., Springer-Verlag, Berlin (1978); "Advances in Carbohydrate Chemistry", Vol. 12, Ed. by M.L. Wolfrom, Academic Press, New York in the chapter The Schardinger Dextrins by Dexter French at p. 189-260; "Cyclodextrins and their Inclusion Complexes" by J. Szejtli, Akademiai Kiado, Budapest, Hungary (1982); I. Tabushi in Acc. Chem. Research, 1982, 15, p. 66-72; W. Sanger, Angewandte Chemie, 92, p. 343-361 (1981); A.P. Croft and R.A. Bartsch in Tetrahedron, 39, p. 1417-1474 (1983); Irie et al. Pharmaceutical Research, 5, p. 713-716, (1988); Pitha et al. Int. J. Pharm. 29, 73, (1986); DE 3,118,218; DE-3,317,064; EP-A-94,157; US-4,659,696; and US-4,383,992.

More recent examples of substituted cyclodextrins include sulfobutylcyclodextrins. Their use is also envisaged in the present invention.

The cyclodextrin used is preferably a β-cyclodextrin, in particular hydroxypropyl-β-cyclodextrin. The most preferred cyclodextrin derivative for use in the compositions of the present invention is hydroxypropyl-β-cyclodextrin having a M.S. in the range of from 0.35 to 0.50 and containing less than 1.5% unsubstituted β-cyclodextrin. M.S. values determined by NMR or IR preferably range from 0.55 to 0.75.

Nevertheless, the choice of cyclodextrin may be directed by the ability of the selected drug compound to be complexed by a particular cyclodextrin - thus the

cyclodextrins with greater affinity for the particular drug compound may be preferred.

In the compositions of the invention, the cyclodextrin is preferably present at 5 to 70% by weight, more preferably 8 to 40%, most preferably 10 to 30% by weight (relative to the total weight of cyclodextrin, acid, organic polymer and drug). The quantity of cyclodextrin used however will generally be dependent on the quantity of drug and the molar ratio of cyclodextrin to drug will preferably lie in the range 5:1 to 1:5, especially 3:1 to 1:2, more especially 2:1 to 1:1.

The acid used in the compositions of the invention may be any of the water-soluble physiologically tolerable acids, in particular any of the inorganic or, more preferably, organic acids conventionally used in the preparation of acid salts of drug compounds, e.g. citric, fumaric, tartaric, maleic, malic, succinic, oxalic, malonic, benzoic, mandelic and ascorbic acids.

Tartaric acid and more especially citric acid are preferred since the salts they form with drug compounds tend to have a reduced tendency to precipitate from aqueous solution. In general however any acid which is not so strong as to cause degradation of the cyclodextrin and yet which is capable, on the addition of water, of generating a low pH environment may be used. The acid may be in liquid (e.g. solution) or solid form; however acids which are solid at ambient conditions in their anhydrous or hydrate forms will generally be preferred.

In the compositions of the invention, the acid will preferably be present at 1 to 95% by weight, preferably 5 to 90% by weight, more preferably 20 to 80%, and especially preferably 35 to 60% by weight (relative to

the total weight of cyclodextrin, drug compound, organic polymer and acid). The amount of acid used will be dependent upon the selected acid and drug compound, but in general an increase in the relative proportion of acid will result in an acceleration of drug dissolution on contact with water. The amount of acid used will normally be at least the amount necessary to form a 1:1 salt with the drug compound.

In general, the acid will form a significant proportion of the composition according to the invention. Thus viewed from a further aspect the invention provides a pharmaceutical composition comprising an organic drug compound, a water-soluble physiologically tolerable acid, a water-soluble physiologically tolerable cyclodextrin and a water-soluble physiologically tolerable organic polymer, characterised in that the weight ratios of drug compound to acid and of drug compound to cyclodextrin are no more than 2:1, preferably no more than 1.5:1, especially preferably no more than 1:1, and particularly preferably no more than 0.9:1, especially no more than 0.5:1.

The organic polymer used in the compositions of the invention may be any of the physiologically tolerable water soluble synthetic, semi-synthetic or non-synthetic organic polymers.

Thus for example the polymer may be a natural polymer such as a polysaccharide or polypeptide or a derivative thereof, or a synthetic polymer such as a polyalkylene oxide (e.g. PEG), polyacrylate, polyvinylpyrrolidone, etc. Mixed polymers, e.g. block copolymers and glycopeptides may of course be used.

It is believed that the effect of the organic polymer arises from an enhancement in viscosity which serves to

stabilize supersaturated solutions of the drug compound on dissolution of the composition of the invention. Thus the polymer conveniently has a molecular weight in the range 500D to 2 MD, and conveniently has an apparent viscosity of 1 to 100 mPa.s when in a 2% aqueous solution at 20°C. For example, the water-soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyakylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectins such as sodium carboxymethylamylopectin,
- chitin derivates such as chitosan,
- heparin and heparinoids,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gum arabic, guargum and xanthan gum,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide, e.g. poloxamers and

poloxamines.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing compositions according to the present invention.

Particularly preferably the organic polymer is a cellulose ether, e.g. methyl cellulose, hydroxyethylmethylcellulose, or hydroxypropylmethylcellulose, for example a Methocel® such as Methocel A, Methocel E, Methocel F, Methocel K, Methocel J or Methocel HB or a Metolose® such as Metolose SM, Metolose SH or Metolose SE. Especially preferably the organic polymer is a hydroxypropylmethylcellulose, e.g. from 5 cps Methocel E to 15000 cps Methocel K15M.

Even very small quantities of the organic polymer serve to achieve a beneficial effect in the compositions of the invention. Thus in the compositions of the invention the organic polymer is conveniently present at 0.05 to 35% by weight, preferably 0.1 to 20%, more preferably 0.5 to 10%, and most preferably 2 to 6% by weight (relative to the total weight of drug compound, acid, cyclodextrin and organic polymer). The content and viscosity grade of the organic polymer both affect the dissolution profile for the drug compound in the compositions of the invention, with increased organic polymer content and/or increased viscosity grade (e.g. 15000 mPa.s in place of 5 mPa.s (mPa.s values being at 2% aqueous solution at 20°C)) both tending to decelerate drug compound dissolution). Accordingly the selection of the identity and quantity of the organic polymer will generally depend upon the dissolution profile that is desired.

The drug compound used in the compositions of the invention may be any organic or inorganic material which is no more than sparingly soluble, i.e. which is sparingly soluble, slightly soluble, very slightly soluble, or practically insoluble in pure water at 21°C (ie. requiring from 30, from 100, from 1000 or from 10000 parts water to put 1 part by weight drug compound into solution).

Examples of such poorly water-soluble compounds that may be used in the compositions of the invention include nifedipine, itraconazole (described in EP-A-6711), saperconazole (see US-A-4916134), (-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one (Compound 40 in WO96/13499), and cisapride (described in EP-A-76530). Other examples include the following:

alpha-Lipoic acid	Carbidopa
8-Methoxypsoralen	Carbocromen
Acetazolamide	Chlordiazepoxide
Acetylsalicyclic	Chloroquine
Allopurinol	Chlorothiazide
alpha.-Tocopherol	chlorpromazine
Amiloride	Chlorprothixene
Ascorbyl palmitate	Chlortalidone
Atenolol	Cimetidine
Benzbromarone	Clenbuterol
Benzthiazide	Clofibrate
Betamethasone	Clomipramine
Bromocriptine	Clonidine
Bromopride	Codergocrine
Buphenine	Cortisone
Bupranolol	Cyclizine

Cyclosporin A
Desipramine
Dexamethasone
Dextropropoxyphene
Diazepam
Diazoxide
Diclofenac
Diclofenamide
Dihydralazine
Diltiazem
Disulfiram
Domeperidone
Doxepine
Ergotamine
Ethacrynic acid
Ethinylestradiol
Ethoxzolamide
Etoposide
Fenbufen
Fenoterol
Fludrocortisone
Flufanamic acid
Flunarizine
Fluphenazine
Furosemide
Gallopamil
Gemfibrozil
Guanethidine
Haloperidol
Hydrochlorothiazide
Hydrocortisone
Hydroflumethiazide
Ibuprofen
Imipramine
Indomethacine
Iron salts
Ketoprofen
Labetalol
Lactose
Lithim salts
Lorazepam
Magnesium salts
Medroxyprogesterone acetate
Mefenamic acid
Melperone
Menadione
Methaqualone
Methyltestosterone
Methylthiouracil
Methylxanthine
Metipranolol
Metoclopramide
Molsidomine
Morphine
Naproxen
Nicargolin
Nifedipine
Nimodipine
Norfenefrine
Nortriptyline
Noscapine
Oxprenolol
Oxymetholone
Oxyphenbutazone
Paclitaxel
Papaverine
Paramethasone
Pentazocine
Pethidine
Phenobarbital
Phenylbutazone

Phytomenadione
Pirenzepine
Polythiazide
Prazosin
Prednisolone
Prednisone
Probenecid
Propranolol
Propylthiouracil
Quinine
Rapamycin
Rescinnamine
Reserpine
Sacbutabarbital
Secobarbital
Sorbitan monolaurate
Sorbitan monooleate
Spironolactone
Stanozolol
Sulfasalazine
Sulfonamide
Sulindac
Sulpiride
Tacrolimus
Tetraglycerol laurate
Thioridazine
Thiothixene
Triamcinolone
Triamteren
Trichloromethiazide
Trifluoperazine
Trifluopromazine
Verapamil

Aciclovir
Amoxicilin
Captopril
Omeprazole
Mosapride
Lansoprazole
Rabeprazole
Clozapine
Cimetidine
Fluoxetine
Fluconazole
Fluvoxamine
Ranitidine
Terfenadine

Drug compounds suitable for use in the compositions of the invention include drugs of all types conventionally administered topically (e.g. in a gel patch) or into an externally voiding body duct, e.g. orally, nasally, aurally, rectally or vaginally. Such drugs include in particular antifungals, calcium channel blockers, antibacterials, antihypertensives, antivirals, analgesics, apolipoprotein B synthesis inhibitors, and drugs which modify transit of gi tract contents (e.g. antidiarrhoea agents or motility promoters).

Indeed, the invention is particularly applicable to poorly water-soluble imidazole, triazole, imidazo-benzazepines, nitrophenyl-pyridine, N,N'-bis-phenyl-piperazine, and N-phenoxyalkyl-piperidine derivatives, e.g. the compounds mentioned above and compounds as described in EP-A-6711, WO96/13499 and EP-A-76530.

The compositions of the invention may conveniently contain the drug compound at 0.1 to 50% by weight, preferably 1 to 35%, more preferably 5 to 30%, especially 8 to 25% and most especially 10 to 15% by weight (relative to the total weight of acid, cyclodextrin, organic polymer and drug compound). The quantity of drug will of course depend upon the desired dissolution profile, the intrinsic solubility of the drug compound and the drug dosage required where the drug is to be delivered in dosage units (e.g. capsules, coated tablets, etc).

Thus for example if the drug is to be delivered in a standard capsule (e.g. with a 900 mg capacity for a glass thermoplastic system as described in the Examples hereto, and the desired drug dose is 100 mg/capsule) then the quantities and natures of the other composition components may be selected to give the desired drug dissolution profile - in general only a small quantity of organic polymer, e.g. 20 to 50 mg, may be necessary, and the balance may be made up from acid and cyclodextrin with the ratio of acid to cyclodextrin being set according to the required dissolution profile, e.g. with 200 to 330 mg cyclodextrin and 450 to 550 mg acid.

Besides the drug compound, the organic polymer, the acid and the cyclodextrin, the compositions of the invention may contain other conventional pharmaceutical

excipients, e.g. flavours, colouring agents, antioxidants, bulking agents, fats, waxes, coating agents, dispersants, suspension fluids (e.g. where the composition coated with a gastric juice resistant coating and dispersed as particles in a suspension fluid such as water or a syrup), etc. Preferably such components when in intimate admixture with the drug compound will make up only a minor proportion of the composition, e.g. 0.01 to 10% by weight (relative to the total weight of acid, organic polymer, cyclodextrin and drug compound). However where the composition of the invention is encapsulated or disposed in a carrier (e.g. a fluid or a solid or semi-solid matrix), the further components not in intimate admixture with the drug compound (e.g. coating or encapsulating materials, dispersion media, etc.) may of course make up a minor or major proportion, e.g. 5 to 95% by weight, of the overall composition.

The compositions of the invention may be prepared by making an intimate admixture of the drug compound, cyclodextrin, acid and organic polymer. This may be effected most straightforwardly by dissolving these components in a liquid solvent therefor and subsequently removing the solvent. Thus viewed from a further aspect the invention provides a process for the preparation of a pharmaceutical composition, said process comprising: dissolving a drug compound, a water-soluble cyclodextrin, a physiologically tolerable water-soluble acid and a physiologically tolerable water-soluble organic polymer in a solvent; removing solvent from the resultant solution; optionally forming the resultant product into desired shapes; and optionally coating the resulting product with a physiologically tolerable coating material.

The solvent used in the process of the invention is

preferably a physiologically tolerable material, suitably an organic solvent such as a C_{1-6} alkanol (e.g. ethanol), acetone, DMF, a linear or cyclic ether (e.g. diethyl ether, dimethyl ether, or THF), cyclohexane, DMSO, etc. or a solvent mixture. For an acid with a high melting point, solvents or solvent mixtures which have high boiling points may conveniently be used; generally however the boiling point of the solvent or solvent system will be no more than about 100°C. Such solvents may be used efficiently in the production of the compositions of the invention and the level of residual solvent will be minimal. The solvent may conveniently be removed by evaporation, e.g. under reduced pressure, and as this may leave some solvent residue (e.g. up to 3% by weight) it is particularly desirable to use a solvent such as ethanol which is a permitted pharmaceutical excipient.

If the drug compound is insoluble or poorly soluble in the solvent of choice, the process of the invention may involve dispersion of microparticles (e.g. nanoparticles having a particle size of 1 to 100 nm) of the drug compound in the solvent rather than full dissolution of the drug compound. If this is done, it is desirable that the drug compound particles be as small as possible. Nanoparticles of insoluble compounds may be prepared for example by various precipitation techniques or by milling with physiologically tolerable inorganic beads, e.g. of zirconia.

The solvent removal may be essentially complete or it may be incomplete, in the former case to produce a solid or a gel-like solid or semi-solid, and in the latter case to produce a viscous fluid which can for example be filled into capsules.

In general, essentially complete solvent removal will be

preferred as the resultant product can then readily be shaped. Shaping may be effected by spray-drying the solution (to provide the product in particulate form), by evaporation of solvent from solution disposed in molds, by molding (e.g. injection molding), by extrusion and the like. In general the product can be formed when hot and allowed to solidify on cooling. The shaped product may likewise be produced in film or sheet form by evaporation or by pouring a heated mass onto a plate and evaporating off the solvent.

In one preferred embodiment the product is shaped by filling into (e.g. by pouring or by extrusion) capsule shells, e.g. of gelatin.

The product may be hygroscopic, and thus may be "tacky" if touched by hand due to its absorption of moisture from the skin. Accordingly it is particularly preferred for the product to be provided with a protective coating to prevent moisture uptake during handling. Such coatings may for example take the form of capsule casings (as described above), tablet coatings, protective film or web coatings, and moisture-proof removable wrappings. Tablet coatings may be applied in conventional manner and may be such as to dissolve in the mouth or stomach (e.g. sugar or sugar/beeswax coatings), or alternatively may be gastric juice resistant polymers (such as the gastric juice resistant Eudragit coatings produced by Röhm GmbH) where it is desired that drug uptake should occur in the intestines. Protective films or webs may for example be used where the product is to be applied topically, e.g. for uptake across the skin or a toe or finger nail. In this event a pad of the composition will generally be disposed between an adhesive upper protective layer and a lower removable layer. An example of a topical application form for application on nails and adjoining tissue, e.g.

for the treatment of fungal infection, is shown in US-A-5181914.

Where the product is produced in particulate form, e.g. by spray-drying, the particles can be loaded into water-tight administration devices (e.g. spray devices or powder dosing devices such as inhalers) for oral, nasal or topical administration of the particulate. Alternatively particulates may be loaded into capsules or mixed with bulking agents and compressed to form tablets. In any event, the particles may additionally be provided with one or more coatings, e.g. to provide a delayed or prolonged release administration forms.

Generally however it will be preferred to shape the product into individual doses and to provide these with a protective coat, e.g. to produce a capsule, coated tablet or film covered pad single dosage unit.

While not wishing to be bound by theory it is thought that the advantageous drug compound dissolution profile for the compositions of the invention is achieved as a result of a combination of the effects of the components of the composition on exposure to water or aqueous body fluids. The water and the acid provide a highly acidic microenvironment in which the solubility of the drug compound is increased. This acidic microenvironment contains the cyclodextrin which is capable of complexing the solubilized drug causing the production of a supersaturated solution of the drug compound and this supersaturated solution is stabilized by the viscosity enhancing effects of the organic polymer which hinders precipitation of the drug as the pH increases as the microenvironment becomes more dilute as more water enters.

Accordingly, in the compositions of the invention, in

place of the cyclodextrin it is considered possible to use other compounds capable of complexing the drug compound, in particular host complexants capable (like cyclodextrin) of producing host:guest complexes with the drug compound may be used. Likewise, for base solubilized drug compounds, a physiologically tolerable water-soluble base (e.g. an inorganic or organic base such as an alkali metal carbonate (eg. sodium carbonate) ethanolamine, diethanolamine, etc.) may be used in place of the acid, and in place of the organic polymer a water-soluble physiologically tolerable macromolecular (e.g. of molecular weight ≥ 1kD) viscosity enhancer may be used; in each case in the quantities specified above for the cyclodextrin, acid and organic polymer respectively.

While the benefits of the compositions of the invention are most pronounced where the drug compound is no more than sparingly soluble, the drug dissolution profiles achievable using the combination of drug, cyclodextrin and acid (or base) are such that particularly improved drug uptake profiles may be achieved even where the drug compound is more soluble. Thus viewed from an alternative aspect the invention provides a pharmaceutical composition comprising in intimate admixture a drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer.

Moreover, where appropriate quantities of cyclodextrin, acid and drug compound are used, it is possible to achieve particularly desirable drug dissolution profiles where the organic polymer is used in very small quantities or even omitted. Thus viewed from a further aspect the invention provides a pharmaceutical composition comprising in admixture a no more than sparingly water soluble organic drug compound, a water-

soluble physiologically tolerable organic acid and a water-soluble physiologically tolerable cyclodextrin, said acid and cyclodextrin being present at 1.5 to 15 (preferably 2 to 10, more preferably 2.5 to 6) parts by weight and 1 to 7 (preferably 1.1 to 5, more preferably 1.25 to 4) parts by weight respectively per part by weight of said drug compound.

As has been mentioned above, the compositions according to the invention can be produced with particularly favourable drug dissolution profiles. Thus dissolution may be sufficiently rapid to ensure substantially complete availability of the drug compound for biological uptake (e.g. from the mouth, nose, stomach or vagina) yet sufficiently slow to provide a more prolonged plasma uptake profile (see for example Figure 1 of the accompanying drawings) e.g. by avoidance of drug reprecipitation before the composition reaches the stomach.

Such a dissolution profile is thus novel and advantageous in its own right and viewed from a further aspect the invention provides a pharmaceutical composition comprising an organic drug compound and at least one water-soluble physiologically tolerable excipient, characterised in that at 5, 15 and 45 minutes after addition of a quantity of said composition containing 100 mg of said drug compound to 600 mL of 0.1N hydrochloric acid at 37°C, from 7 to 25 (preferably 10 to 20, especially 12 to 18) %, 45 to 70 (preferably 50 to 65, especially 54 to 63) % and at least 96 (preferably at least 97, especially at least 98) % respectively of said drug compound is in solution in said hydrochloric acid.

In determining the dissolution profiles set out above, the composition is placed without a coating or with a

rapidly soluble coating (e.g. a gelatin capsule shell) in 0.1 N HCl and the mixture is stirred using the USP-method with a paddle, apparatus 2, at a speed of 100 rpm.

The compositions according to the invention may be in any form convenient for topical administration or administration into an externally voiding body cavity (e.g. nose, lungs, mouth, ear, stomach, rectum or vagina). Typical administration forms include patches, tablets, buccal tablets, lozenges, ear-plugs, nose plugs, coated tablets, capsules, suppositories, chewing gum, gels, powders, granules, syrups and dispersions, although patches and powders and more especially capsules and coated tablets are preferred. The drug dosage will depend upon the drug compound as well as the species and size of the subject being treated. Typically, dosages will be 0.5 to 1.2, preferably 0.8 to 1.05 times the conventional dosages for the selected drug compound administered by the same route.

The invention will now be described further with reference to the following non-limiting Examples and the accompanying drawings, in which:

Figures 1A and B are graphs showing plasma concentrations of the drug (-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one administered in a composition according to the invention and in a conventional administration form (sugar particles coated with the drug and loaded in a gelatin capsule); and

Figure 2 is a dissolution profile for a composition according to the invention.

Example 1

Glass thermoplastic system composition preparation

The following ingredients are mixed in a 250 mL glass flask:

Drug compound (e.g. itraconazole)	20 g
Citric acid monohydrate	100 g

Anhydrous ethanol (100 mL) is added. The glass flask is placed on a steam bath (bain marie) and stirred at 70°C until the drug and acid are completely dissolved (about 10 minutes). Thereafter the following ingredients are added:

Hydroxypropyl-β-cyclodextrin	50 g
Hydroxypropylmethylcellulose (2910.5 mPa.s)	10 g

The flask is placed on the steam bath and stirred at 70°C until dissolution is complete (about 70 minutes). The solution is then poured onto cleaned stainless steel plates which are then placed in a drying oven for 2 hours at 80°C under vacuum and subsequently for 40°C under vacuum overnight. The plates are then heated to 80°C and the gel residue is scraped off and filled into 900 mg capacity gelatin capsules (size no. 0).

Example 2

Composition preparation

Analogously to Example 1, gelatin capsules having the following relative weights of components are prepared:

(A)	100 mg	Itraconazole
	500 mg	citric acid monohydrate

	275 mg	hydroxypropyl-β-cyclodextrin
	25 mg	Methocel E5
(B)	100 mg	Itraconazole
	500 mg	citric acid monohydrate
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	Methocel E5
(C)	100 mg	Itraconazole
	500 mg	citric acid monohydrate
	225 mg	hydroxypropyl-β-cyclodextrin
	75 mg	Methocel E5
(D)*	200 mg	Methyl 6,11-dihydro-11-[1-[2-[4-(2-quinolinylmethoxy)phenyl]ethyl]-4-piperidinylidene]-5H-imidazo[2,1-b]-[3]benzazepine 3-carboxylate
	650 mg	citric acid monohydrate
	250 mg	hydroxypropyl-β-cyclodextrin
(E)	100 mg	(-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one
	500 mg	citric acid monohydrate
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	Methocel E5

* For example 2(D) the composition is loaded into 1100 mg gelatin capsules.

The dissolution profiles of the gels of Example 2(A), (B) and (C) are shown in Figure 2 of the accompanying drawings. These were determined by placing one capsule containing 100 mg of itraconazole in 300 mL of stirred

0.1 N HCl at 37°C and observing the percentage of dissolved drug compound at times 0, 5, 15, 30, 45 and 60 minutes (stirring was effected using the USP-method with paddle, apparatus 2, 100 rpm). For Example 2(E), with 100 mg drug compound added to 600 mL of 0.1 N HCl at 37°C, the mean percentages of drug compound in solution at 5, 15, 30 and 45 minutes were 17.22, 61.18, 92.73 and 98.67 respectively (stirring was effected using the USP-method with paddle, apparatus 2, 100 rpm).

The dissolution profile of Example 2(E) was compared with that of a conventional capsule dosage form in which the gelatin capsule is loaded with sugar particles coated with 100 mg of (-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one. The capsules were placed in 10 mL of 0.1 N HCl at 37°C in glass vials and shaken in a mechanical shaker (100 strokes per minute) and the percentage of drug compound in solution after 0, 30 and 60 minutes was determined. The results are set out in Table 1 below.

Table 1

Percentage of drug compound in solution

Time	Example 2(E)	Conventional Capsule
0	0	0
30	91.26	15.54
60	101.90	18.39

This clearly shows how much more readily the drug compound is made bioavailable by the compositions of the invention.

Example 3

Effect of organic polymer on supersaturation stability

Aqueous solutions of hydroxyproyl-β-cyclodextrin (HPBCD) and Methocel E5 in 300 mL 0.1 N HCl at 37°C were prepared having the concentrations set out in Table 2. The solutions were stirred using the USP-method with paddle, apparatus 2, 150 rpm.

Table 2

Sample	HPBcD (mg)	Methocel E5 (mg)
1	250	250
2	500	0
3	250	500
4	500	500
5	0	250
6	500	250
7	0	0
8	250	0
9	0	500

To these solutions, with stirring, a concentrated solution of itraconazole in DMF (50 mg/mL) was added dropwise until precipitation was observed. Subsequently the concentration of dissolved itraconazole expressed in mg% (ie. the number of mg dissolved in 100 mL) was observed at 0, 30, 60 and 120 minutes. The results are set out in Table 3 below:

Table 3

Percentage of drug compound in solution

Sample / Time (minutes)	1	2	3	4	5	6	7	8	9
0	59.52	72.10	58.95	75.47	42.65	75.27	42.60	60.95	42.95
30	62.02	74.40	62.05	78.12	44.85	80.17	44.10	62.92	45.20
60	62.52	70.37	62.50	79.47	45.40	80.40	44.97	64.07	46.00
120	62.79	45.82	63.90	80.77	46.55	81.25	31.32	33.65	47.05
HPBCD: Methocel ratio	1:1	2:0	1:2	2:2	0:1	2:1	0:0	1:0	0:2

These results clearly demonstrate (i) the solubilizing effect of the cyclodextrin (Samples 2, 6 and 4 show the highest initial itraconazole concentrations, followed by Samples 8, 1 and 3, with Samples 7, 5 and 9 showing the lowest initial concentrations) and (ii) the stabilizing effect of the organic polymer (Samples 2, 8 and 7 show the greatest drop in itraconazole concentrations over 120 minutes, etc).

Example 4

Extended release formulation

Analogously to Example 1, gelatin capsules were prepared containing the following:

41.55 mg	Cisapride
508.45 mg	citric acid monohydrate
250 mg	hydroxypropyl-β-cyclodextrin
100 mg	Methocel K15M

This formulation has a much slower dissolution rate than the compositions of Example 2. However the rate of dissolution is much more close to linear with time and shows much less dependence on the pH of the dissolution medium.

Example 5

Nail gel

A gel for application to nails or hooves to effect antifungal treatment is made with the following composition:

Itraconazole	250 mg
Citric acid monohydrate	2083 mg
Hydroxypropyl-β-cyclodextrin	333 mg
Hydroxypropylmethylcellulose (Methocel E5)	83 mg
Anhydrous ethanol	2 mL

Example 6

Body uptake

The plasma concentrations of R 103757 were determined in healthy humans at 0, ½, 1, 1½, 2, 3, 4, 6, 8 and 12 hours after oral administration of 100 mg (-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one as (i) a 5 mg/mL oral solution containing 25% hydroxypropyl-β-cyclodextrin solution administered under fasting conditions, (ii) a conventional capsule containing (-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-

(4-chlorophenyl]-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one coated onto sugar particles administered under fasting conditions, (iii) a conventional capsule containing (-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one coated onto sugar particles administered after a standard breakfast, (iv) a capsule according to Example 2(E) administered under fasting conditions and (v) a capsule according to Example 2(E) administered after a standard breakfast.

The "standard breakfast" comprised four slices of bread, one slice of ham, one slice of cheese, butter, jelly and two cups of coffee or tea with milk and/or sugar if desired. The 100 mg dose of (-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one was administered just after such a breakfast.

Blood samples of 10 mL were taken to obtain 5 mL plasma. The blood samples were taken, collected in heparinized tubes, and centrifuged at 1000g for 10 minutes within 2 hours of collection. Plasma was transferred into plastic tubes, which were sealed and stored at -70°C until assayed.

The results are shown in Figures 1(A) and 1(B) which presents drug concentrations as a function of time. As can be seen, the conventional capsule performs significantly worse than the solution even with

fasting. However the capsule according to the invention outperforms the solution after 3 hours whether or not the recipient has fasted and, most surprisingly, completely outperforms the solution where the recipient has not fasted.

Claims

1. A pharmaceutical composition comprising a no more than sparingly water-soluble drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer.

2. A pharmaceutical composition comprising an organic drug compound, a water-soluble physiologically tolerable acid, a water-soluble physiologically tolerable cyclodextrin and a water-soluble physiologically tolerable organic polymer, characterised in that the weight ratios of drug compound to acid and of drug compound to cyclodextrin are no more than 2:1.

3. A pharmaceutical composition comprising in intimate admixture a drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer.

4. A pharmaceutical composition comprising in admixture a no more than sparingly water soluble organic drug compound, a water-soluble physiologically tolerable organic acid and a water-soluble physiologically tolerable cyclodextrin, said acid and cyclodextrin being present at 1.5 to 15 parts by weight and 1 to 7 parts by weight respectively per part by weight of said drug compound.

5. A pharmaceutical composition comprising an organic drug compound and at least one water-soluble physiologically tolerable excipient, characterised in that at 5, 15 and 45 minutes after addition of a quantity of said composition containing 100 mg of said

drug compound to 600 mL of 0.1N hydrochloric acid at 37°C, from 7 to 25%, 45 to 70% and at least 96% respectively of said drug compound is in solution in said hydrochloric acid.

6. The use of a drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and optionally a physiologically tolerable water-soluble organic polymer for the manufacture of a pharmaceutical composition according to any one of claims 1 to 5 for use in a method of therapy or diagnosis of the human or non-human animal body.

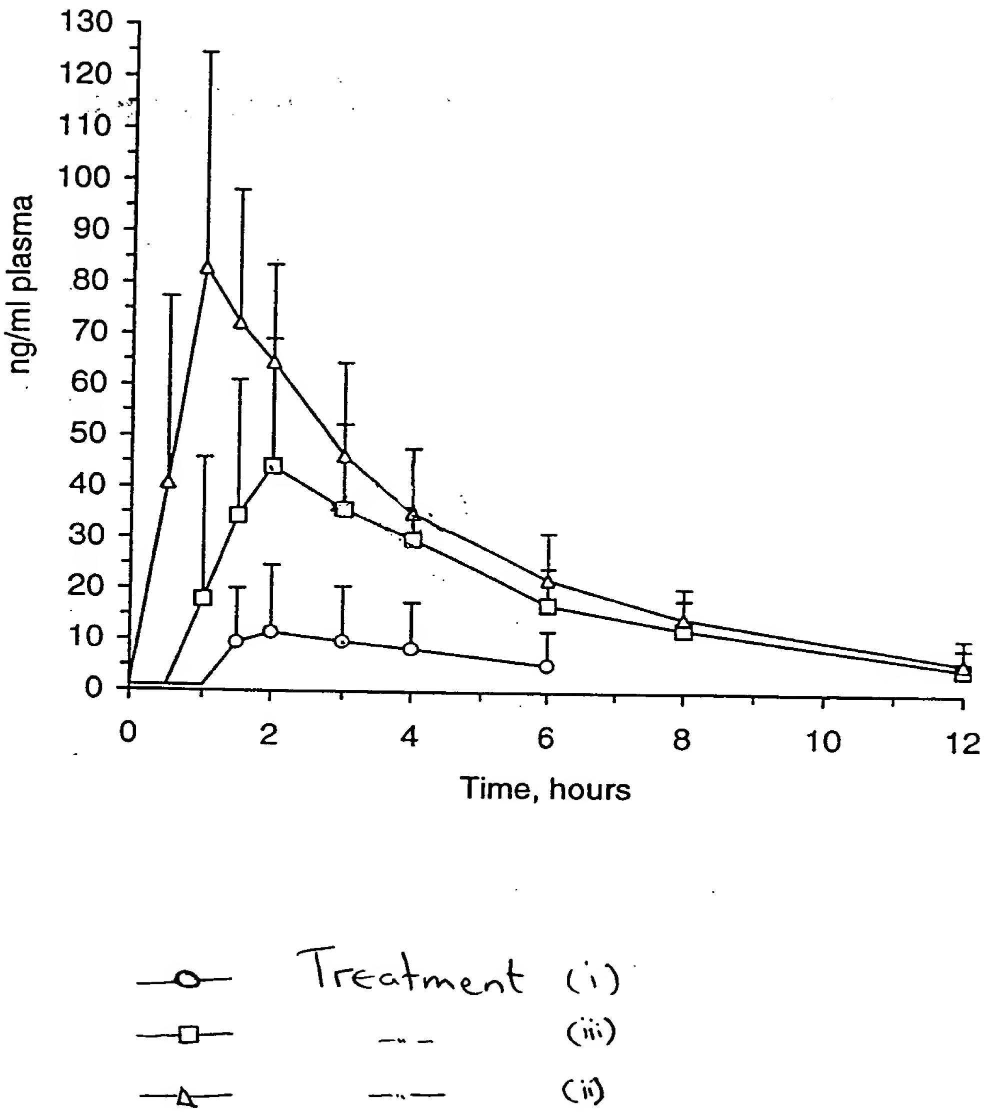
7. A method of therapy or diagnosis of the human or non-human animal body which comprises administering to said body a therapeutically or diagnostically effective dose of a pharmaceutical composition, the improvement comprising using as said composition a composition according to any one of claims 1 to 5.

Abstract

Composition

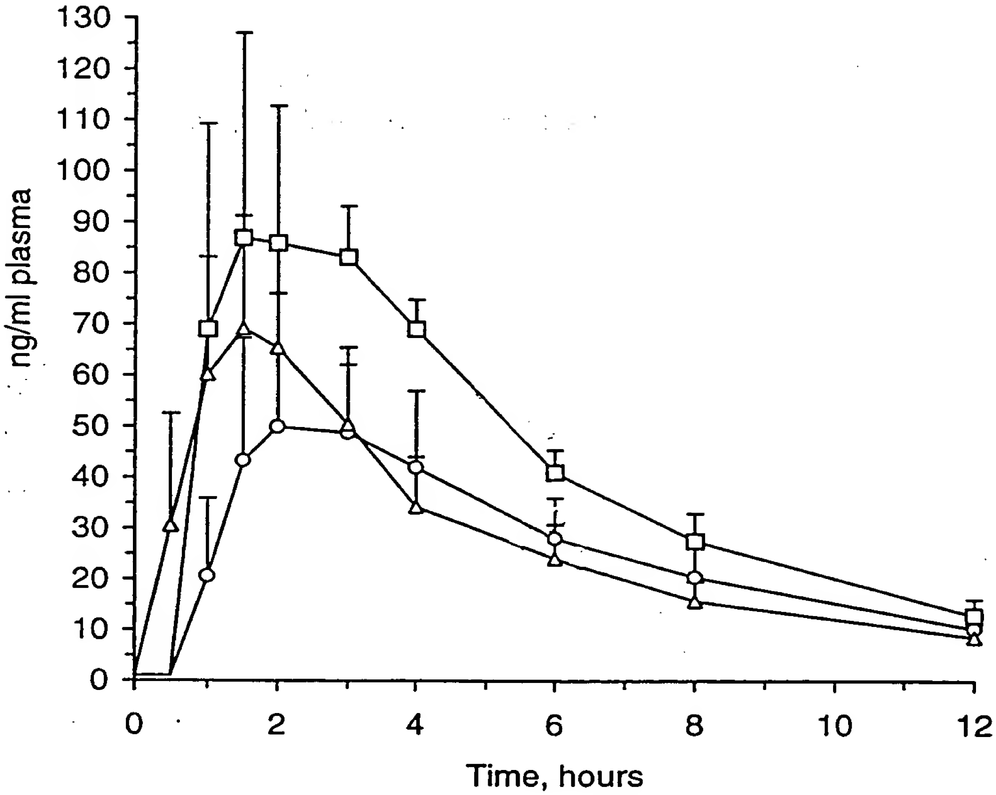
The invention provides a novel pharmaceutical composition comprising a no more than sparingly water-soluble drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer.

FIGURE 1A



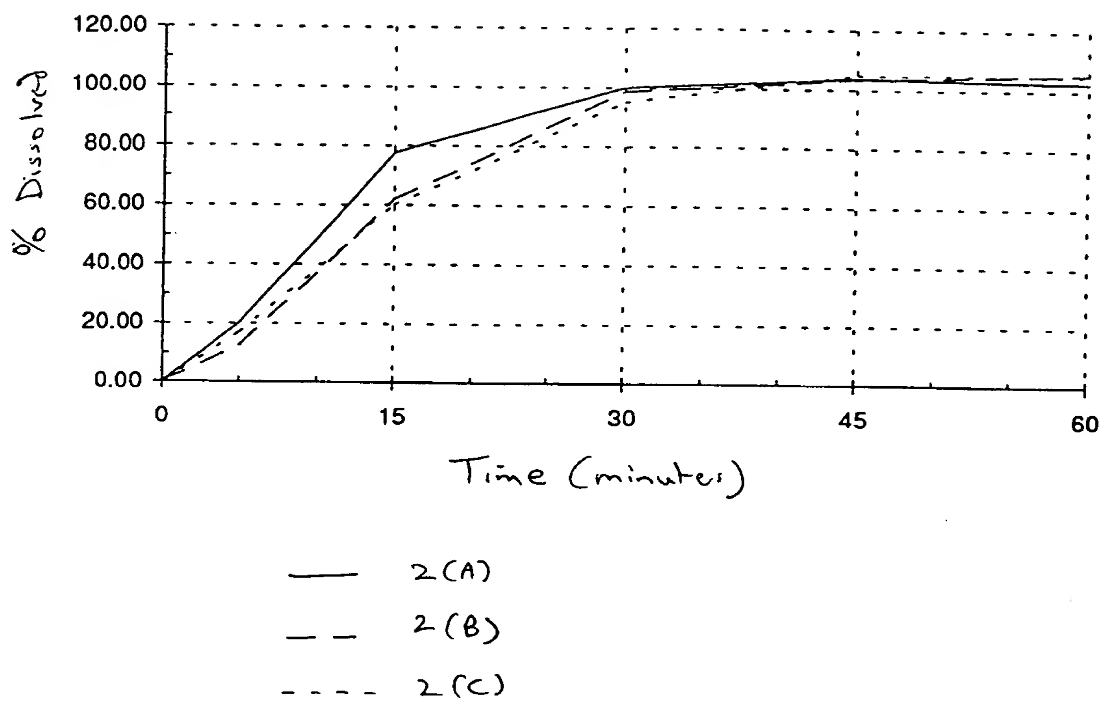
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ng/ml plasma
0
2
4
6
8
10
12
Time, hours
Treatment (i)
" (iii)
" (ii)

FIGURE 1B



Treatment (iv)
" (v)
" (i)

FIGURE 2


120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
15
30
45
60
Time (minutes)
2(A)
2(B)
2(C)

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